
Application Reviews by RFA/Genomics/GC1R-06673

REVIEW REPORT FOR CIRM RFA 12-06R GENOMICS CENTERS OF EXCELLENCE AWARDS (R)

GC1R-06673: Center of Excellence for Stem Cell Genomics

GWG Overall Center Recommendation: Tier 1

GWG Overall Final Score: 88

GWG Data Center Recommendation: Tier 1

GWG Data Center Final Score: 90

CIRM Staff Recommendation: Fund overall genomics center together with the associated Data Coordination and Management component. Furthermore, staff recommends removal of Center Initiated Project #3, as recommended by the Grants Working Group (GWG), and retention of Center Initiated Project #2, as recommended by the GWG Minority Report. Total requested funds for this award are \$33,327,072.

Public Abstract (provided by applicant)

The Center of Excellence in Stem Cell Genomics will bring together investigators from seven major California research institutions to bridge two fields - genomics and pluripotent stem cell research. The projects will combine the strengths of the center team members, each of whom is a leader in one or both fields. The program directors have significant prior experience managing large-scale federally-funded genomics research programs, and have published many high impact papers on human stem cell genomics. The lead investigators for the center-initiated projects are expert in genomics, hESC and iPSC derivation and differentiation, and bioinformatics. They will be joined by leaders in stem cell biology, cancer, epigenetics and computational systems analysis. Projects 1-3 will use multi-level genomics approaches to study stem cell derivation and differentiation in heart, tumors and the nervous system, with implications for understanding disease processes in cancer, diabetes, and cardiac and mental health. Project 4 will develop novel tools for computational systems and network analysis of stem cell genome function. A state-of-the-art data management program is also proposed. This research program will lead the way toward development of the safe use of stem cells in regenerative medicine. Finally, Center resources will be made available to researchers throughout the State of California through a peer-reviewed collaborative research program.

Statement of Benefit to California (provided by applicant)

Our Center of Excellence for Stem Cell Genomics will help California maintain its position at the cutting edge of Stem Cell research and greatly benefit California in many ways. First, diseases such as cardiovascular disease, cancer, neurological diseases, etc., pose a great financial burden to the State. Using advanced genomic technologies we will learn how stem cells change with growth and differentiation in culture and can best be handled for their safe use for therapy in humans. Second, through the collaborative research program, the center will provide genomics services to investigators throughout the State who are studying stem cells with a goal of understanding and treating specific diseases, thereby advancing treatments. Third, it will employ a large number of "high tech" individuals, thereby bringing high quality jobs to the state. Fourth, since many investigators in this center have experience in founding successful biotech companies it is likely to "spin off" new companies in this rapidly growing high tech field. Fifth, we believe that the iPSC and information resources generated by this project will have significant value to science and industry and be valuable for the development of new therapies. Overall, the center activities will create a game-changing network effect for the state, propelling technology development, biological discovery and disease treatment in the field.

Review Summary

This application for a Genomics Center of Excellence Award represents a consortium of investigators from seven major academic and nonprofit research organizations across the State of California. Four independent Center-Initiated Projects (CIPs) have been proposed, encompassing studies ranging from basic stem cell biology and differentiation, to investigations of disease mechanism and development of novel technologies for analysis of genome function. The application includes a Data Coordination and Management program, which will be led by a key Center collaborator. A Collaborative Research Plan has also been proposed to enable investigators

throughout the state to share Center resources by participating in peer-reviewed collaborative research.

Center Organization and Operational Plan

- The proposed Director and Co-Director are international leaders in their respective fields, with outstanding track records in developing and applying new genomics techniques as well as managing large, complex and successful collaborations.
- All relevant infrastructure and related resources are in place for providing a comprehensive menu of cutting-edge genomics assays.
- Reviewers noted outstanding and appropriate institutional support including very substantial matching funds from multiple participating institutions.
- The coherent and comprehensive organizational plan takes advantage of existing physical cores for data production and analysis.
- Although some reviewers expressed minor concerns that the multiple, geographically separated components of this large and interdependent program could pose an administrative challenge, overall, reviewers expressed much confidence in the demonstrated abilities and collaborative experience of the program leaders for achieving a shared vision.

Collaborative Research Projects

- Plans for soliciting high impact collaborative research projects from the community are well developed and realistic, with several judicious features including cost analysis, project management, and scientific guidance for successful applicants.
- Review procedures are well described and appropriate for ensuring the highest standards of scientific evaluation.
- Plans for providing assistance and advice on experimental design and sequencing implementation to collaborating researchers were considered excellent.
- While the external members of the Advisory and Review Committee are not named, reviewers had confidence that an excellent cadre of experts from outside of California would be successfully recruited.

CIP-1

This project aims to establish a biological repository of well characterized, induced pluripotent stem cell (iPSC) lines from patients with either of two forms of familial cardiomyopathy, as well as healthy controls. Using genomics approaches, the applicants seek to validate the utility of this resource for modeling cardiovascular disease and drug toxicity, and to identify novel mechanisms underlying these disorders. Various genomics approaches will also be used to define the extent and origin of heterogeneity amongst individual iPSC lines. The applicants plan to share the iPSC lines and genomics data with the academic community.

- The proposed iPSC resource would be of considerable value to the scientific community.
- Understanding the origin of variation amongst iPSC lines and how it impacts cell phenotype is of great importance, although it was not clear from the application how novel insights would be readily translated to improved derivation protocols that limit stochastic variation.
- While not particularly innovative, the experimental plan is highly feasible and builds largely on existing expertise, routine methods, and established laboratory work-flow.
- The project leaders are eminently qualified, with relevant track records of success in the fields of stem cell biology, functional genomics, cardiology, population genetics and bioinformatics.
- The conditions to be studied, familial dilated cardiomyopathy and familial hypertrophic cardiomyopathy, are prevalent and thus represent important medical burdens.
- Reviewers criticized the inclusion of Aim 3, which aims to evaluate drug safety using iPSCs. The connection between drug toxicity and familial cardiomyopathy was not clearly established in the proposal, nor bolstered by preliminary data.
- There is little discussion of the current knowledge base on the genetics of familial cardiomyopathy nor how that information would impact experimental design and interpretation.

- Some reviewers felt the proposal would have been strengthened by greater inclusion of studies to link genomic and gene expression data to cellular defects in morphology and contractile behavior and to patients' disease characteristics. Others, however, thought it appropriate for a Genomics Center to generate and make available a resource of iPSC lines and genomics data for others with an interest in cardiac disease to help analyze.

CIP-2

The primary goal of this project is to apply single cell profiling techniques towards systematically comparing the heterogeneous cell subpopulations within normal and pathological tissues of the human brain and pancreas. Data generated from these studies will be used to reconstruct cellular hierarchies by lineage and disease, to elucidate mechanisms of pathogenesis, and to identify gene expression and epigenetic markers for detecting abnormal cells within a cell population. The results of these studies will be made available to the scientific community through an openly accessible database.

- The proposal lacked important details concerning which cell phenotypes will be isolated for study. Furthermore, reviewers strongly questioned whether meaningful conclusions could be drawn from the proposed analyses, as the cell populations to be compared have not been defined at the functional level.

- The proposal lacked detail as to how the specific comparisons to be made could be applied towards understanding the pathologies to be investigated. For example, key aspects of Down Syndrome brain pathology develop prior to the time frame in which the specimens for analysis are to be collected. While other aspects of neural pathology may still be relevant for study, those were neither articulated nor addressed in the application.

- Although the general notion of analyzing lineage relationships using single cell technologies is significant and innovative, it is not clear how the analysis of the adult tissues chosen will shed light on stem/progenitor biology; this is not well addressed in the application. For instance in the pancreas, there is significant debate about the nature and presence of stem/progenitor populations in the adult organ. There was nothing convincing in the application to indicate a specific familiarity with the biology of the pancreas.

- While reviewers acknowledged significant shortcomings in the biology to be explored, some believed this team is likely to extract interesting information from the proposed comparisons, especially in the case of tumor versus normal tissues.

- The proposal afforded little discussion of potentially obfuscating factors and how they would affect data interpretation, such as the tremendous heterogeneity within an individual pancreatic tumor or between tumors from different patients, or how the cell profiles might be affected when obtained from autopsied specimens as opposed to living tissues.

- The proposed study is a technological tour-de-force, exploiting highly innovative, cutting edge techniques that are unparalleled around the world. Reviewers judged this team uniquely qualified to undertake a project of such magnitude and ambition.

- The project leadership is the key strength of this application, representing a powerful merging of expertise in technology development, cancer biology, and computational modeling. Notably absent, however, is an expert in pancreatic biology, whose knowledge may be critical to acquiring meaningful insights from Aim 2.

A motion was made to remove this center-initiated project and requested funds from the application. Reviewers reiterated concerns that the sophistication and power of the cutting edge methods were undercut by weaknesses in the specific biological questions to be addressed. Some reviewers felt that despite the flaws, the impact of utilizing these powerful technologies and developing them for the community is sufficiently worthy of support, and necessary to push the field forward. Panelists suggested that if possible, funds for an eliminated Center-Initiated Project might be redirected towards the Collaborative Research Plan component.

The motion carried, but a minority position was stated. While acknowledging flaws, the minority believed that this technology and these investigators have a great potential to impact stem cell research in California and provide opportunities for innovation. Further, they believed that it is important to the integrity of the Genomic Center as a whole to have multiple Center Initiated Projects affiliated with it.

CIP-3

The goal of this project is to characterize iPSCs from monozygotic (identical) twins discordant for schizophrenia (i.e. only one twin is affected) to elucidate the molecular basis of this disorder. The applicants propose to generate neuronal progenitors and differentiated neurons from 6 twin pairs, 3 discordant for schizophrenia, and characterize their genome, epigenome and chromatin landscape. Findings will be correlated with single cell gene expression analysis and validated in functional assays.

- The proposed study is not sufficiently powered to produce meaningful information about the biology or genetics of schizophrenia, especially in the context of discordant monozygotic twin pairs. Given the current evidence that a very large number of genetic variants contribute to schizophrenia risk, combined with the added complexity of potential effects of epigenetic changes at many of those genomic locations, reviewers considered this shortcoming to be a fundamental flaw.
- If epigenetic differences between discordant twins drive development of schizophrenia, many of those disease-specific epigenetic marks may be specific to the affected person's brain and may not be replicated in the fibroblast-based iPSC models. This reduces enthusiasm for the rationale underlying this proposal.
- The research team is outstanding, bringing together leading experts in neuroscience, reprogramming, epigenomics and cutting edge technologies.
- The proposal tackles a fast-moving and important area of research. The plans to extensively characterize derived neuronal cells using state of the art approaches and highly feasible differentiation protocols are commendable.

A motion was made to remove this center-initiated project and requested funds from the application. The motion carried without discussion.

CIP-4

This project aims to adapt existing tools and develop new computational methods for translating data from stem cell genomics studies into models of molecular networks and other mechanisms with predictive ability. Key outcomes for this project include a database of molecular interactions relevant to stem cells (CIRM Molecular Network Database); a database of gene attributes in the context of biological processes in stem cells (Stem Cell Gene Ontology); new software tools for identifying functional biomarkers and suggesting gene manipulations for influencing cell fate; and a web-based engine for predicting cell fate status based on molecular profiles.

- This project was considered a major strength of the overall proposal. Computational tools such as those proposed are highly significant to the field and essential to the success of the proposed Center of Excellence.
- Reviewers appreciated the balance between applying existing tools and innovative development of algorithms.
- The project leaders have outstanding and complementary credentials in computational biology and bioinformatics, and a highly relevant track record in the development and implementation of tools for organizing and utilizing large-scale datasets.
- Specific aims are highly achievable. Successful outcomes will prove useful not only to the stem cell community in California, but also to the broader field of systems biology.

Data Coordination and Management

- Reviewers considered the Data Coordination and Management Center to be a major strength of the application, possessing all of the necessary infrastructure and activities to support planned data capacity for all CIRM-funded Center(s) and collaborative projects.
- The leader of this center component is a pioneer in the field and has an outstanding track record in the proposed activities.
- The team directing this center has extensive experience in the coordination and management of genomics data.
- Although there was minor concern that the coordination of data from geographically dispersed centers would be a challenge, reviewers were confident in the ability of the team, with its extensive experience, to overcome potential problems.
- Appropriate and detailed strategies for achieving uniform standard operating protocols for genomic data handling are proposed.

Conflicts

- Richard Gibbs
- Maynard Olson

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